# General

## Guideline Title

New antiretroviral drugs: maraviroc, raltegravir, etravirine, and rilpivirine.

## Bibliographic Source(s)

New York State Department of Health. New antiretroviral drugs: maraviroc, raltegravir, etravirine, and rilpivirine. New York (NY): New York State Department of Health; 2011 Nov. 8 p. [14 references]

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: New York State Department of Health. New antiretroviral drugs: maraviroc, raltegravir, and etravirine. New York (NY): New York State Department of Health; 2010 Jun. 6 p.

# Recommendations

## Major Recommendations

Definitions for the quality of the evidence (I-III) and strength of recommendation (A-C) are provided at the end of the "Major Recommendations" field.

What's New – November 2011 Update

- The U.S. Food and Drug Administration (FDA) has issued new rash and hypersensitivity warnings regarding raltegravir (see *Section III: Raltegravir* in the original guideline document and the recommendation below).
- The new non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine has been approved by the FDA for treatment in antiretroviral therapy (ART)-naïve patients (see *Section V: Rilpivirine* in the original guideline document and the recommendation below).

Introduction

Prescribers should consult with a clinician with extensive experience with antiretroviral therapy (ART) and management before initiating treatment with maraviroc, raltegravir, etravirine, or rilpivirine. These drugs should optimally be used as part of a regimen with at least two fully active agents plus the new agent.

Maraviroc

Maraviroc should be prescribed only for patients with CCR5-tropic virus, as determined by a tropism assay that is performed at the time that therapy is considered. (AII) Maraviroc should not be used outside of clinical trials in patients with dual/mixed- or CXCR4-tropic virus. (AII)

Key Point:

Maraviroc may be used as part of a salvage regimen in treatment-experienced, CCR5-tropic patients when resistance or side effects have limited the use of other available agents. Maraviroc also has been recently approved by the FDA for use in initial regimens for treatment-naïve, CCR5-tropic patients.

Raltegravir

Clinicians should perform resistance testing before changing from a protease inhibitor (PI)-boosted regimen to raltegravir (see the "HIV resistance assays" section of the National Guideline Clearinghouse [NGC] summary of the New York State Department of Health [NYSDoH] guideline Antiretroviral Therapy). (AII)

Clinicians should discontinue raltegravir in patients who develop signs or symptoms of severe skin reactions or hypersensitivity reactions.

Key Point:

Raltegravir has been recently approved by the FDA for use in initial regimens for treatment-naïve patients. Raltegravir may also be used as part of a salvage regimen in treatment-experienced patients when resistance or side effects have limited the use of other available agents.

Etravirine

Etravirine should be used only as part of a salvage ART regimen in treatment-experienced patients for whom the use of other available agents is limited because of resistance to previously approved NNRTIs. (AII)

For regimens that include both etravirine and a protease inhibitor, clinicians should co-administer etravirine with only one of the following ritonavir-boosted protease inhibitors: lopinavir, darunavir, or saquinavir. (AII)

Rilpivirine

Rilpivirine is recommended only for ART-naïve adults in combination therapy when an alternative to the preferred NNRTI, efavirenz, is being considered. (AII)

Clinicians should use caution when prescribing rilpivirine for patients with HIV ribonucleic acid (RNA) levels >100,000 copies/mL because of the increased risk for virologic failure compared with efavirenz (see Table 2 in the original guideline document). (AII)

Rilpivirine should be used with at least two other fully active agents, such as tenofovir plus emtricitabine or abacavir plus lamivudine (for information regarding selection of an initial ART regimen, see the "Selecting an Initial Antiretroviral Regimen" section of the NGC summary of the NYSDoH guideline Antiretroviral Therapy). (AII)

Key Point:

A fixed-dosed combination pill, Complera, containing rilpivirine, tenofovir, and emtricitabine, is available (see Complera full prescribing information from Gilead Sciences).*

*When prescribing the combination drug Complera, clinicians should be aware that a vitamin preparation has a similar trade name (i.e., Complere); confirmation that the correct prescription is dispensed to patients should be ensured.

Definitions:

Quality of Evidence for Recommendation

I. One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
II. One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes

III. Expert opinion

Strength of Recommendation

A. Strong recommendation for the statement
B. Moderate recommendation for the statement
C. Optional recommendation

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

Human immunodeficiency virus (HIV) infection

## Guideline Category

Management

Treatment

## Clinical Specialty

Allergy and Immunology

Family Practice

Infectious Diseases

Internal Medicine

## Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Public Health Departments

## Guideline Objective(s)

To provide updated guidelines for the use of new antiretroviral drugs maraviroc, raltegravir, etravirine, and rilpivirine in human immunodeficiency virus (HIV)-infected patients

## Target Population

Human immunodeficiency virus (HIV)-infected patients (both treatment-naïve and treatment-experienced)

## Interventions and Practices Considered

1. Maraviroc and raltegravir in treatment-experienced or treatment-naïve patients
2. Etravirine in treatment-experienced patients
3. Rilpivirine in treatment-naïve patients

## Major Outcomes Considered

- Effectiveness of treatment
- Side effects of treatment
- Drug interactions
- Drug resistance

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

MEDLINE was searched up to November 2011 with use of relevant key words. Results were limited to publication years 2008-2011. The update focused on the use of rilpivirine in human immunodeficiency virus (HIV)-infected patients. The following were cited: 1) recent clinical trial data; 2) U.S. Food and Drug Administration (FDA) labeling and announcement about rilpivirine; and 3) manufacturer's package inserts for rilpivirine and the combination antiretroviral therapy pill Complera, which includes rilpivirine.

## Number of Source Documents

Not stated

## Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Quality of Evidence for Recommendation

I. One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
II. One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes

III. Expert opinion

## Methods Used to Analyze the Evidence

Review

## Description of the Methods Used to Analyze the Evidence

Not stated

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

AIDS Institute clinical guidelines are developed by distinguished committees of clinicians and others with extensive experience providing care to people with human immunodeficiency virus (HIV) infection. Committees* meet regularly to assess current recommendations and to write and update guidelines in accordance with newly emerging clinical and research developments.

The Committees* rely on evidence to the extent possible in formulating recommendations. When data from randomized clinical trials are not available, Committees rely on developing guidelines based on consensus, balancing the use of new information with sound clinical judgment that results in recommendations that are in the best interest of patients.

*Current committees include:

- Medical Care Criteria Committee
- Committee for the Care of Children and Adolescents with HIV Infection
- Dental Standards of Care Committee
- Mental Health Guidelines Committee
- Committee for the Care of Women with HIV Infection
- Committee for the Care of Substance Users with HIV Infection
- Physicians' Prevention Advisory Committee
- Pharmacy Advisory Committee

## Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

A. Strong recommendation for the statement
B. Moderate recommendation for the statement
C. Optional recommendation

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

## Description of Method of Guideline Validation

All guidelines developed by the Committee are externally peer reviewed by at least two experts in that particular area of patient care, which ensures depth and quality of the guidelines.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Appropriate use of the new antiretroviral drugs maraviroc, raltegravir, etravirine, and rilpivirine

## Potential Harms

- *Maraviroc*. Main side effects include cough, fever, colds, rash, muscle and joint pain, stomach pain, and dizziness. Maraviroc should not be used outside of clinical trials in patients with dual/mixed- or CXCR4-tropic virus. Maraviroc should not be co-administered with the CYP3A inducer St. John's wort (*Hypericum perforatum*) or products containing St. John's wort. Maraviroc should not be prescribed for patients with severe renal impairment or end-stage renal disease (ESRD) who are receiving potent CYP3A inducers or potent CYP3A inhibitors. Patients with severe renal impairment or ESRD not receiving potent CYP3A inducers or inhibitors may require dose adjustments for maraviroc to avoid cardiovascular risks associated with postural hypotension. U.S. Food and Drug Administration (FDA) Pregnancy Category: B
- *Raltegravir*. Main side effects include rash and diarrhea. Severe, potentially life-threatening, and fatal skin reactions have been reported, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Discontinue immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop, including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema. FDA Pregnancy Category: C
- *Etravirine*. Main side effects include mild to moderate rash, which may resolve with continued treatment. Stevens-Johnson syndrome, erythema multiforme, and/or hepatic failure occurred rarely; the development of any of these conditions warrants immediate discontinuation. Etravirine should not be co-administered with: other non-nucleoside reverse transcriptase inhibitors (NNRTIs); any unboosted protease-inhibitor (PI) (i.e., administered without ritonavir); certain boosted PIs: tipranavir/ritonavir (note: the clinical significance is unknown for fosamprenavir/ritonavir and atazanavir/ritonavir). Because etravirine is a substrate of hepatic CYP450 enzymes and an inducer/inhibitor of these enzymes, significant drug interactions can occur with concurrent medications. See the etravirine package insert or the "HIV Drug-Drug Interactions" in the "Availability of Companion Documents" field, for information on drug interactions. FDA Pregnancy Category: B
- *Rilpivirine*. Main side effects include depression, insomnia, headache, and rash. Dizziness occurred less frequently in rilpivirine-treated patients than in those receiving efavirenz; fat redistribution, immune reconstitution syndrome, and possible prolonged QTc interval are also possible adverse reactions. Rilpivirine should not be co-administered with: other NNRTIs; carbamazepine, oxcarbazepine, phenobarbital, phenytoin; rifabutin, rifampin, rifapentine; esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole; the CYP3A inducer St. John's wort (*Hypericum perforatum*) or products containing St. John's wort; dexamethasone (long-term use); drugs that can significantly prolong QTc interval. Rilpivirine should be co-administered with caution with a drug with a known risk for torsade de pointes. FDA Pregnancy Category: B (note: no adequate and well-controlled or pharmacokinetic studies of rilpivirine use in pregnant women have been conducted).

*Maraviroc, raltegravir, etravirine, and rilpivirine* have not been studied in pregnant women. Clinicians who are treating human immunodeficiency virus (HIV)-infected pregnant women should report cases of prenatal exposure to antiretroviral therapy medications to the

Antiretroviral Pregnancy Registry.

# Contraindications

## Contraindications

- Maraviroc should not be used outside of clinical trials in patients with dual/mixed-tropic virus.
- Maraviroc should not be prescribed for patients with severe renal impairment or end-stage renal disease (ESRD) who are receiving potent CYP3A inducers or potent CYP3A inhibitors.

# Qualifying Statements

## Qualifying Statements

When formulating guidelines for a disease as complex and fluid as human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), it is impossible to anticipate every scenario. It is expected that in specific situations, there will be valid exceptions to the approaches offered in these guidelines and sound reason to deviate from the recommendations provided within.

# Implementation of the Guideline

## Description of Implementation Strategy

The AIDS Institute's Office of the Medical Director directly oversees the development, publication, dissemination and implementation of clinical practice guidelines, in collaboration with The Johns Hopkins University, Division of Infectious Diseases. These guidelines address the medical management of adults, adolescents and children with human immunodeficiency virus (HIV) infection; primary and secondary prevention in medical settings; and include informational brochures for care providers and the public.

Guidelines Dissemination

Guidelines are disseminated to clinicians, support service providers and consumers through mass mailings and numerous AIDS Institute-sponsored educational programs. Distribution methods include the HIV Clinical Resource website, the Clinical Education Initiative (CEI), the AIDS Educational Training Centers (AETC) and the HIV/AIDS Materials Initiative. Printed copies of clinical guidelines are available for order from the New York State Department of Health (NYSDoH) Distribution Center.

Guidelines Implementation

The HIV Clinical Guidelines Program works with other programs in the AIDS Institute to promote adoption of guidelines. Clinicians, for example, are targeted through the CEI and the AETC. The CEI provides tailored educational programming on site for health care providers on important topics in HIV care, including those addressed by the HIV Clinical Guidelines Program. The AETC provides conferences, grand rounds and other programs that cover topics contained in AIDS Institute guidelines.

Support service providers are targeted through the HIV Education and Training initiative which provides training on important HIV topics to non-physician health and human services providers. Education is carried out across the State as well as through video conferencing and audio conferencing.

The HIV Clinical Guidelines Program also works in a coordinated manner with the HIV Quality of Care Program to promote implementation of HIV guidelines in New York State. By developing quality indicators based on the guidelines, the AIDS Institute has created a mechanism for measurement of performance that allows providers and consumers to know to what extent specific guidelines have been implemented.

Finally, best practices booklets are developed through the HIV Clinical Guidelines Program. These contain practical solutions to common problems related to access, delivery or coordination of care, in an effort to ensure that HIV guidelines are implemented and that patients receive the highest level of HIV care possible.

## Implementation Tools

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Getting Better

Living with Illness

## IOM Domain

Effectiveness

# Identifying Information and Availability

## Bibliographic Source(s)

New York State Department of Health. New antiretroviral drugs: maraviroc, raltegravir, etravirine, and rilpivirine. New York (NY): New York State Department of Health; 2011 Nov. 8 p. [14 references]

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2008 Apr (revised 2011 Nov)

## Guideline Developer(s)

New York State Department of Health - State/Local Government Agency [U.S.]

## Source(s) of Funding

New York State Department of Health

## Guideline Committee

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## Financial Disclosures/Conflicts of Interest

Not stated

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: New York State Department of Health. New antiretroviral drugs: maraviroc, raltegravir, and etravirine. New York (NY): New York State Department of Health; 2010 Jun. 6 p.

## Guideline Availability

Electronic copies: Available from the New York State Department of Health AIDS Institute Web site .

## Availability of Companion Documents

The following are available:

- Table 2: HIV drug-drug interactions. New York (NY): New York State Department of Health; 2008 Apr. Electronic copies: Available from the New York State Department of Health AIDS Institute Web site .
- Current controversies in antiretroviral therapy. CME course. Available from the Clinical Education Initiative Web site .
- New drugs and new strategies in the treatment of HIV disease. CME course. Available from the Clinical Education Initiative Web site .
- HIV medication errors. CEM course. Available from the Clinical Education Initiative Web site .

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on September 2, 2008. This summary was updated by ECRI Institute on September 4, 2009 following the U.S. Food and Drug Administration advisory on Intelence (etravirine). This NGC summary was updated by ECRI Institute on April 19, 2010. This NGC summary was updated by ECRI Institute on December 14, 2010. This NGC summary was updated by ECRI Institute on January 30, 2012. This summary was updated by ECRI Institute on April 13, 2012 following the U.S. Food and Drug Administration advisory on Statins and HIV or Hepatitis C drugs.

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